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(54) Opthalmic cyclosporin compositions

(57) Ophthalmic compositions comprising a cyclosporin, e.g. Ciclosporin, as active ingredient, and a vegetable oil, preferably corn oil, and a petroleum jelly, preferably white petrolatum, as carrier. The compositions are useful for topical ophthalmic application to the eye and surrounding tissues.

GB 2 224 205 A

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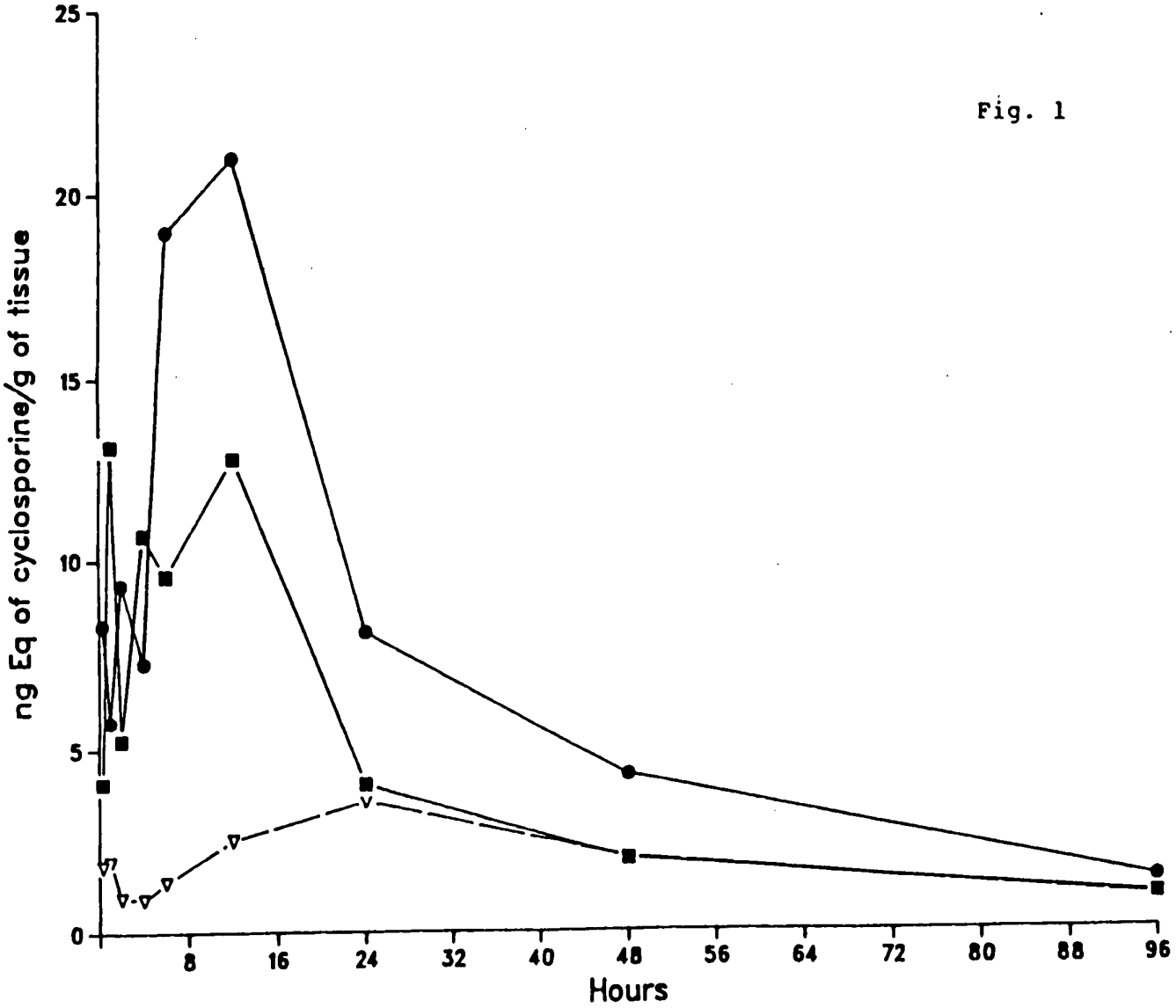
Fig. 1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ng Eq of cyclosporine/g of tissue
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Hours

Fig. 2

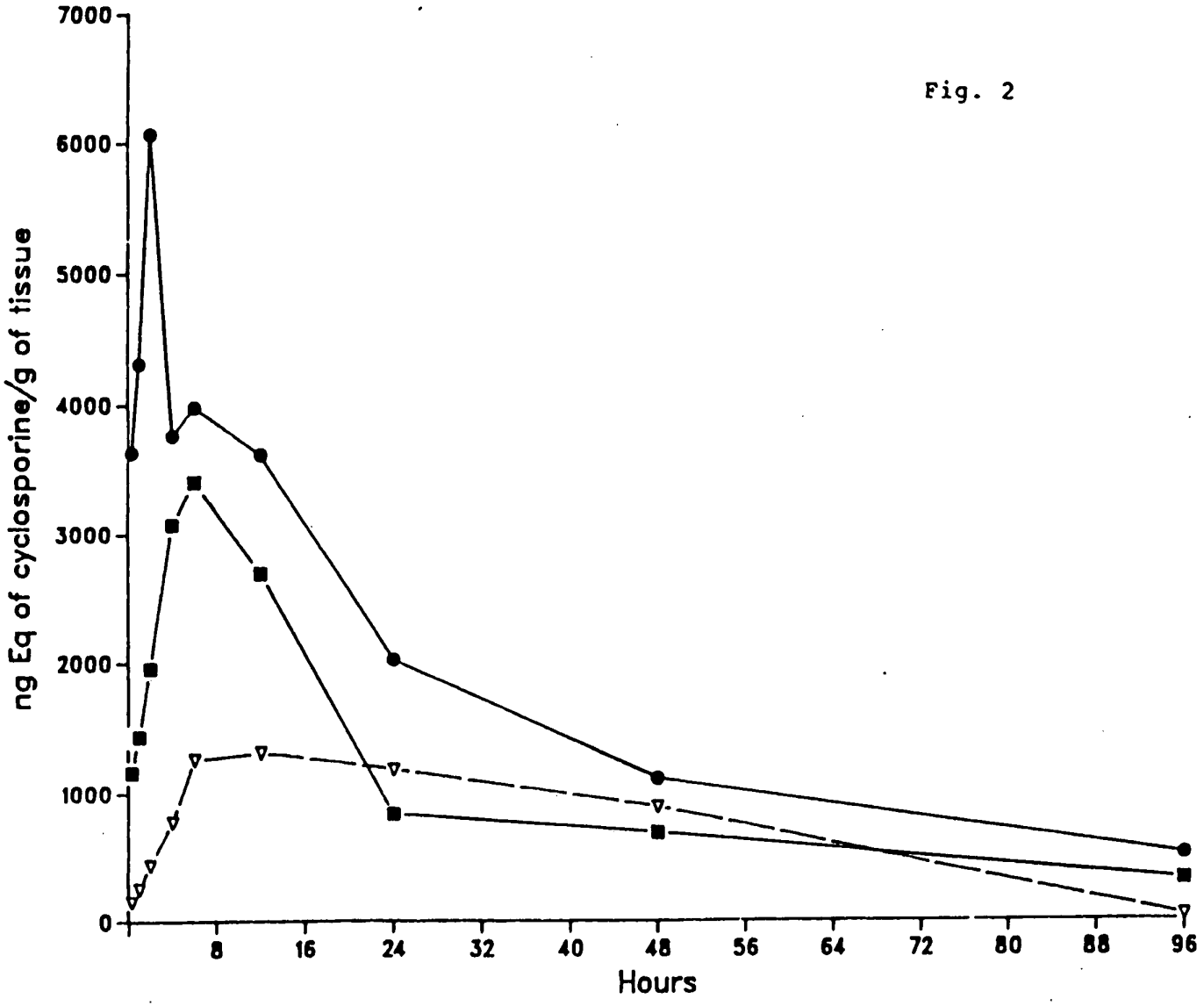
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Fig. 3

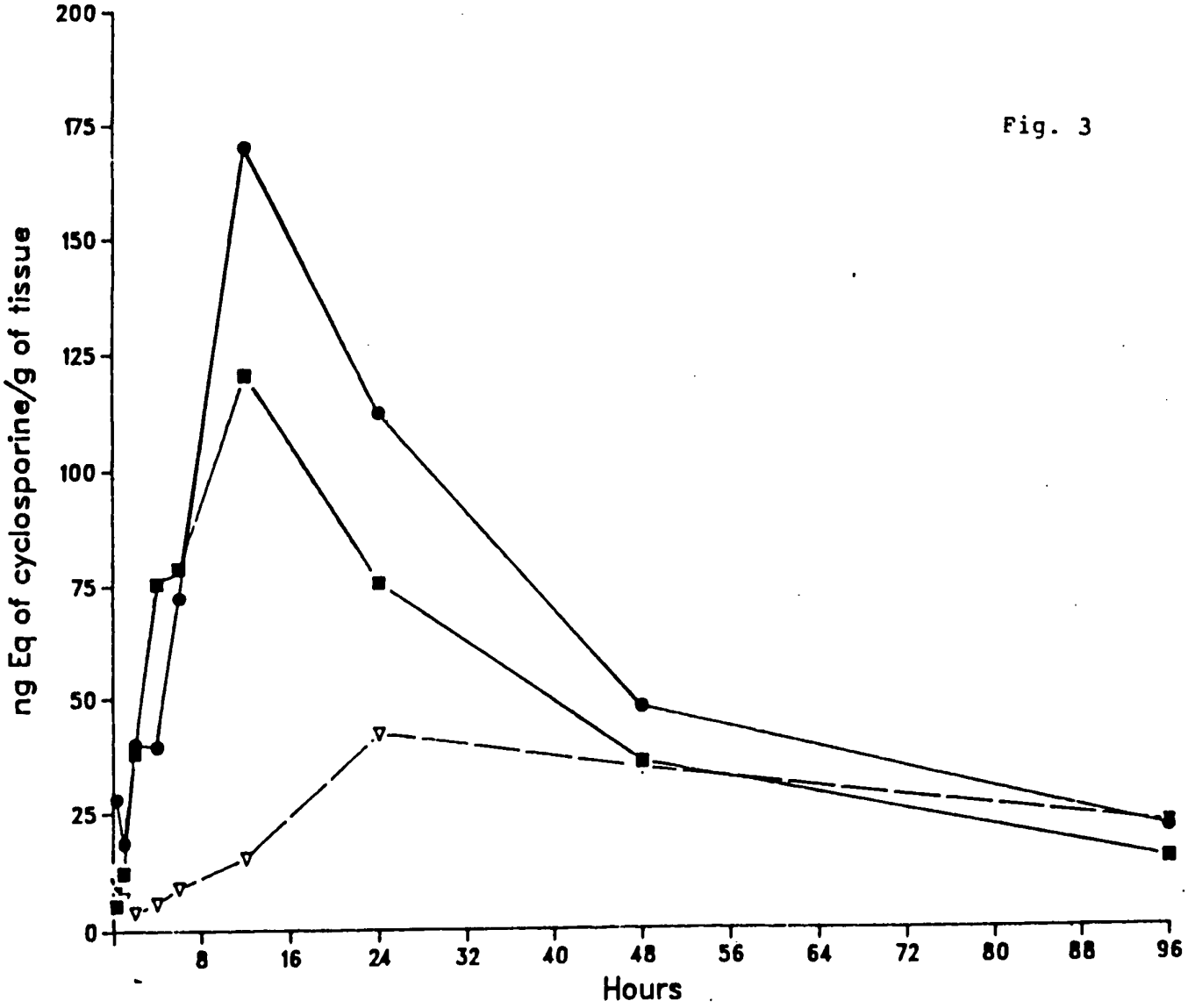
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Fig. 4

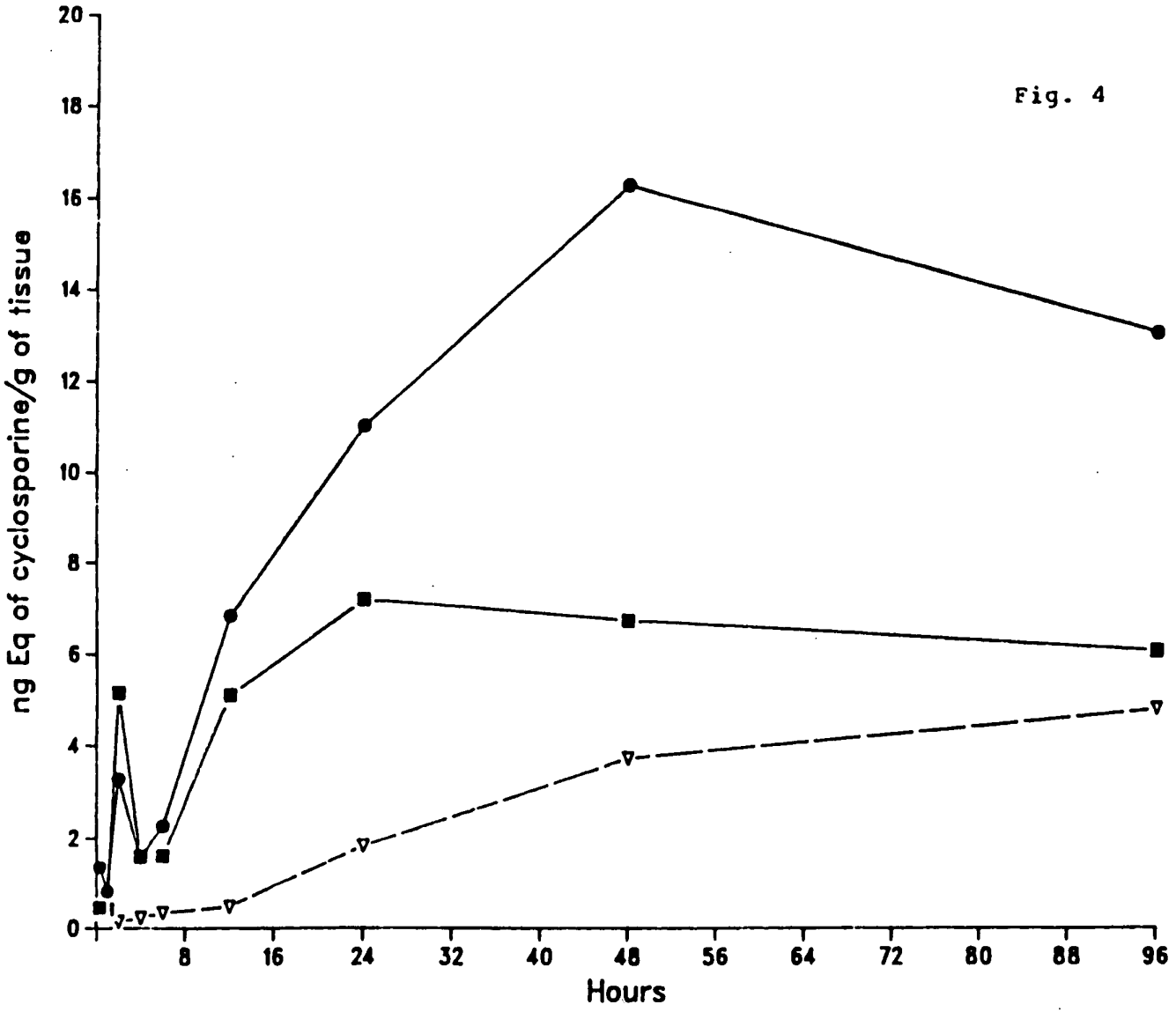
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Fig. 5

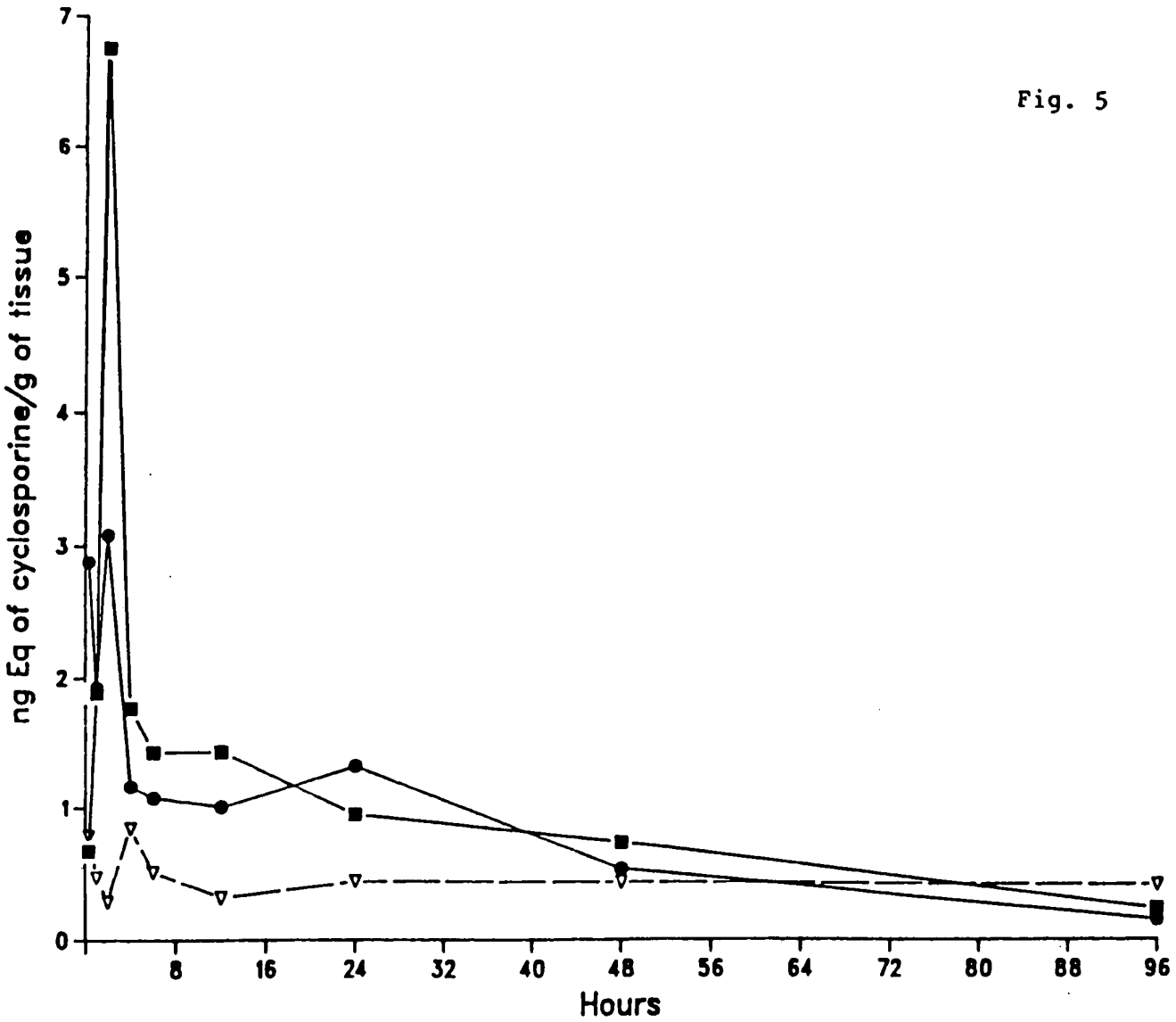
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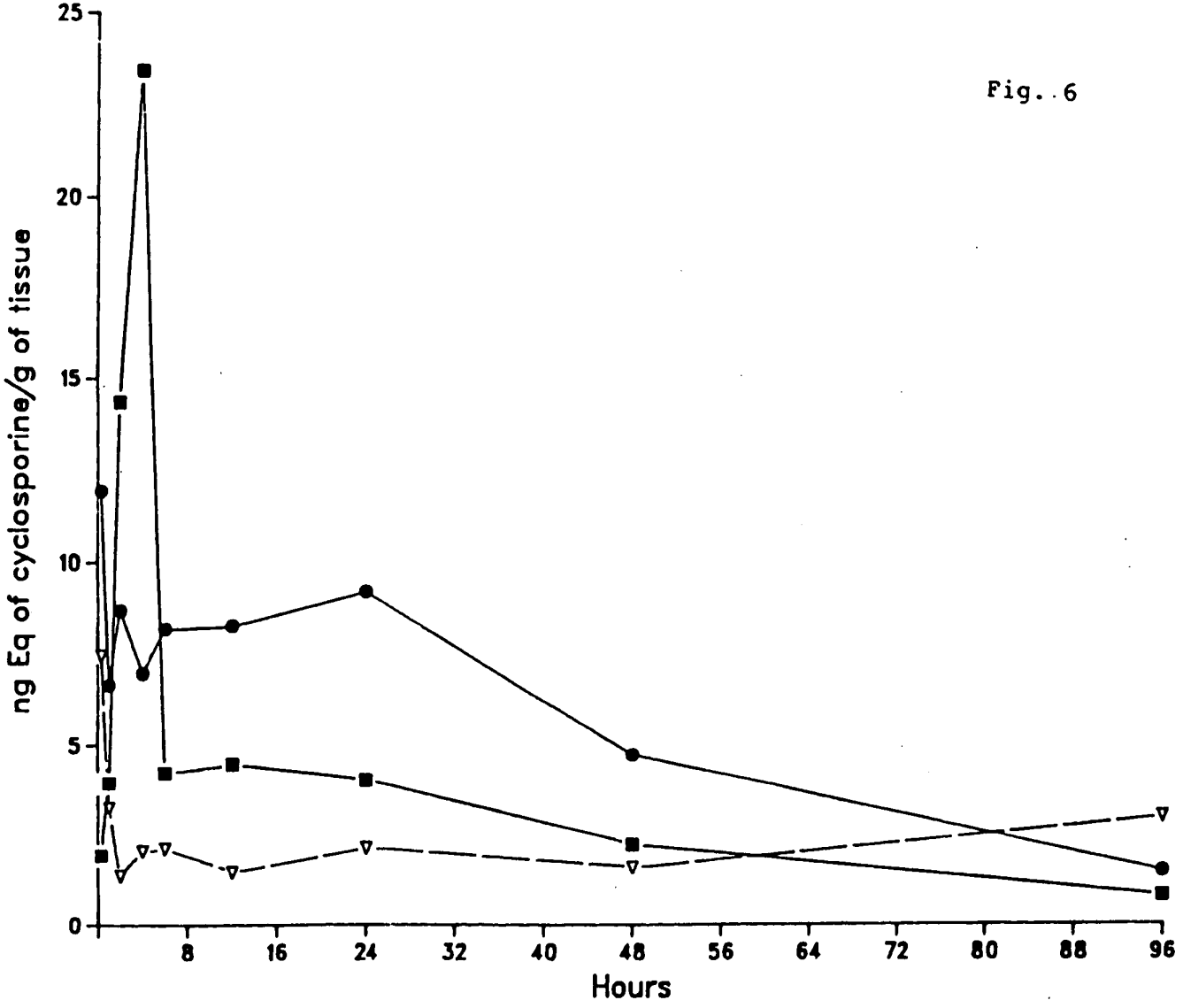
Fig..6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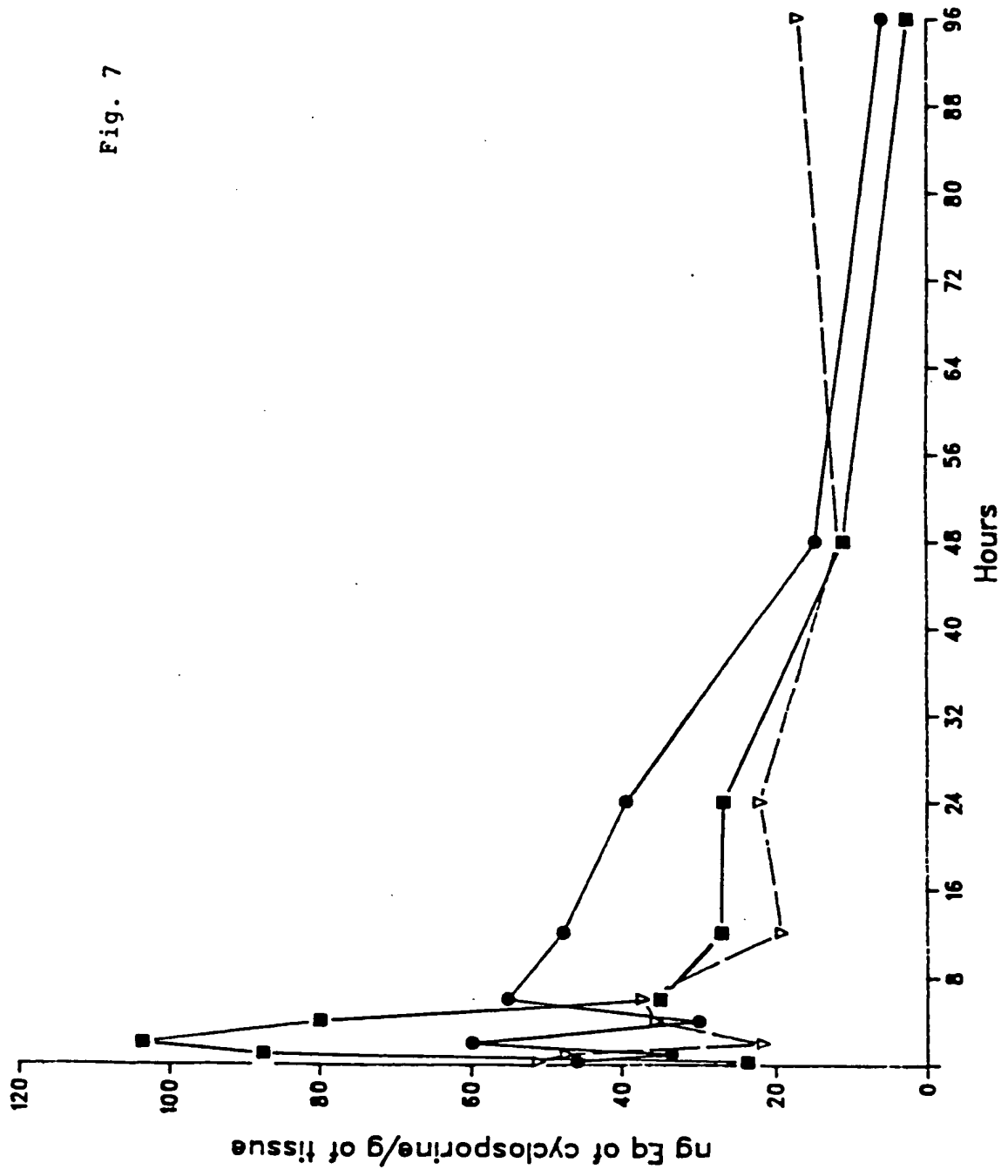
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Hours

Fig. 7

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CYCLOSPORIN OPHTHALMIC COMPOSITIONS

The present invention relates to novel ophthalmic compositions, i.e. pharmaceutical compositions for administration to the eye, comprising a cyclosporin as active ingredient and suitable for the treatment of diseases and conditions of the eye and surrounding areas.

The cyclosporins comprise a large and recognised class of peptide compounds having pharmaceutical utility, for example immunosuppressant, anti-inflammatory, and/or anti-parasitic activity and/or activity in abrogating tumor resistance to antineoplastic or cytostatic drug therapy. The cyclosporins include, for example, naturally occurring fungal metabolites, such as the cyclosporins A, B, C, D and G, as well as a wide variety of synthetic and semi-synthetic cyclosporins, for example the dihydro- and iso-cyclosporins (see e.g. US Patents Nos. 4,108,985; 4,210,581 and 4,220,641), [(D)-Ser]^{8}--Ciclosporin (see USP 4,384,996), [O-acetyl-(D)Ser]^{8}-Ciclosporin (see USP 4,764,503), [β-fluoro-(D)Ala]^{8}-Ciclosporin (see UK Patent Application 2,206,119A), [Val]^{2}-[(D)methylthio-Sar]^{3}- and [Dihydro-MeBmt]^{1}-[Val]^{2}-[(D)methylthio-Sar]^{3}-Ciclosporin [see USP 4,703,033] and very many more.

Of the cyclosporins, the most widely investigated to date is cyclosporin A, also known and referred to hereinafter as Ciclosporin and commercially available under the Registered Trade Mark SANDIMMUN or SANDIMMUNE. Ciclosporin has been shown to suppress selectively a variety of T-lymphocyte functions, including prevention of maturation and expression of sensitized T-lymphocytes in cell mediated immune responses, and is now successfully and widely used in the suppression of organ transplant rejection. Ciclosporin has also been used systemically in the treatment of intraocular inflammatory or autoimmune diseases, such as uveitis. However, because of the side

effects associated with systemic therapy, Ciclosporin has had only limited use in treating such conditions of the eye.

Effective topical administration of Ciclosporin to the eye would reduce or eliminate to a large extent the systemic side effects by restricting activity to the locus of the condition being treated and proposals to this effect have been made, (see e.g. USP 4,649,047). However, utility and effectiveness of Ciclosporin in treating diseases and conditions of the eye has remained hindered by the lack of a suitable composition which is acceptable or effective for topical use. A composition is required, which does not cause patient discomfort and which permits a convenient administration regimen, that is, does not require unduly frequent administration, while providing adequate drug substance delivery both to the external and, in particular, the internal regions of the eye.

Similar considerations apply to other cyclosporins known from the art, e.g. proposed for use as immunosuppressants or anti-inflammatory agents, for example cyclosporin G, also known and referred to hereinafter as [Nva]^2-Ciclosporin.

The present invention provides novel ophthalmic compositions comprising a cyclosporin as active ingredient which meet difficulties hitherto encountered in the art, e.g. as described above. The compositions of the invention are intended for topical application, i.e. for application to or at the surface of the eye, e.g. to the cornea or corneal epithelium, or to the immediate areas surrounding the eye, for example the inner surfaces of the upper or lower lid.

Applied topically as aforesaid, the compositions of the invention are useful for the treatment of diseases or conditions of the eye or of the surrounding or associated organs or tissues, for example the tear glands and ducts, especially immune mediated or inflammatory diseases or conditions. More especially the compositions of the invention are useful for the treatment of diseases or conditions which involve undesirably elevated immuno-response or inflammatory reaction or event

as a component or part of their etiology, in particular autoimmune diseases of the eye. Diseases and conditions which may be treated with the compositions of the invention include, for example uveitis (both anterior and posterior), chronic keratitis, conjunctivitis (including in particular vernal conjunctivitis), vernal keratoconjunctivitis, keratoconjunctivitis sicca, and keratoplasty (i.e. use in relation to corneal transplant), as well as inflammatory or immune mediated conditions induced by ocular surgery in general. The compositions of the invention may also be employed for the induction or maintainance of tearing, for example where tear-function is impaired, e.g. in consequence of any disease or condition as aforesaid.

The ophthalmic compositions of the invention are surprisingly found to cause little or no irritation or patient discomfort and to provide a therapeutic effect at convenient application rates in the corneal and internal regions of the eye, including the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina, or sclera or in surrounding organs or tissues of the eye, for example the tear duct or tear gland.

More particularly the present invention provides in a first aspect:

A) An ophthalmic composition comprising a cyclosporin as active ingredient and comprising (1) an ophthalmically acceptable vegetable oil and (2) an ophthalmically acceptable petroleum jelly as carrier medium.

The compositions of the invention are intended for topical ophthalmic application, i.e. application to the surface of the eye, e.g. to the cornea or corneal epithelium, or to the immediate surrounding regions of the eye.

By "ophthalmically acceptable" is meant appropriate or allovable for administration to the eye, e.g. safe for topical ophthalmic application at dosages to be administered.

Preferred cyclosporins for use in the compositions of the invention are cyclosporins having immunosuppressant or anti-inflammatory activity, e.g. as hereinbefore described, in particular Ciclosporin. A further preferred cyclosporin for use in the compositions of the invention is [Nva]^2-Ciclosporin. The compositions of the invention are suitably in the form of an ointment with the defined components (1) and (2) comprising the ointment base.

The cyclosporin, e.g. Ciclosporin, is suitably present in the compositions of the invention in an amount of from about 0.01 to about 10%. (Unless otherwise indicated, all percentages herein and in the accompanying claims are by weight based on the total weight of the composition.) Preferably the cyclosporin is present in an amount of from about 0.05 to about 10%, especially from about 0.05 to about 5%, more preferably from about 0.1 to about 2.5%. Most preferably the cyclosporin is present in an amount of about 0.1, 0.5, 1.0 or 2.0%.

Component (1) [vegetable oil] is suitably present in the compositions of the invention in an amount of at least 25%. Suitably component (1) is present in an amount of from about 25 to about 65%, preferably from about 25 to about 45%, more preferably from about 35 to about 45%, and especially about 40 to about 45%.

Component (2) [petroleum jelly] is suitably present in the compositions of the invention in an amount of at least 25%, preferably at least 50%. Suitably component (2) is present in an amount of from about 25 to about 65%, preferably from about 50 to about 65%, more preferably from about 50 to about 60%, and especially from about 50 to about 55%.

Components (1) and (2) are suitably present in the compositions of the invention in a ratio of from about 1:2 to 2:1 p.p.w., e.g. about 1:1 p.p.w..

Component (1) may comprise any appropriate vegetable oil including, e.g. olive oil, arachis oil, corn oil, castor oil or sesame oil or

mixtures thereof. Preferably however, component (1) comprises corn oil, e.g. as described in the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (herein "HPE"), joint publication of the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, at page 91.

Component (2) may comprise any appropriate petroleum jelly product, e.g. as available under the names white pretolatum (USP = United States Pharmacopoeia), white soft paraffin (BP/EP = British/European Pharmacopoeias), white petroleum jelly or petroleum jelly or under the names petrolatum yellow (USP), yellow soft paraffin (BP/EP), yellow petrolatum or yellow petroleum jelly - for further definition see HPE, p.p. 194-195. Especially preferred as component (2) are white petrolatum products, e.g. having a Color (Maximum, Lovibond Color - 2" Cell) = ca. 0.5 to 18Y, 0.5R.

Compositions in accordance with the invention also suitably comprise (3) an emulsifier. Suitable components (3) include any ophthalmically acceptable emulsifier, e.g. as known in the art. Preferred emulsifiers for use in the compositions are non-ionic emulsifiers, in particular non-ionic lanolin derivatives or extracts, especially lanolin alcohols (see HPE, p. 164) or sterol-based emulsifiers generally. Examples of suitable emulsifiers for use in the compositions of the invention are products such as known and commercially available under the Trade Name Amerchol, in particular the products Amerchol 400, C, CAB, H9, L-99, 4-500 and RC and especially Amerchol CAB. [For further definition of the above products see Fiedler, "Lexikon der Hilfstoffe, 3rd Edition (1989), p.p. 138-139].

Components (3) when present are suitably present in the compositions of the invention in an amount of from about 0.5 to about 10%, preferably from about 0.5 to about 5%, more preferably from about 1 to 2.5%, e.g. about 2%.

Compositions in accordance with the invention may also include any further components suitable for use in ophthalmic preparations, for

example preserving or anti-microbial agents. In particular they will suitably comprise (4) a preserving agent, chlorobutanol (e.g. as anhydrous chlorobutonal) - see HPE, p.p. 72-73 - being particularly suitable. Such additional components, e.g. components (4), when present will suitably be present in amounts of up to about 5.0%, more suitably up to about 2.0%, e.g. from about 0.01 to about 2.0% or to about 5.0%, preferably from about 0.1 to about 1.0%, e.g. ca. 0.5%. Compositions in accordance with the present invention may thus suitably comprise, e.g. the following ingredients in the relative indicated amounts:

CYCLOSPORIN [e.g. CICLOSPORIN OR [Nva]^2-CICLOSPORIN]	0.01 to 10%
(1)	25 to 65%
(2)	25 to 65% preferably 50 to 65%
(3)	0.5 to 10%
(4)	0.1 to 5%

plus any further components to a total of 100%, whereby components (1) and (2) are preferably present in a ratio of about 1:2 to 2:1 p.p.w., and whereby preferred ranges for individual components may independently be selected from those hereinbefore indicated. The following example is illustrative of the compositions of the invention.

EXAMPLE

COMPONENT	
CYCLOSPORIN (e.g. CICLOSPORIN)	2.0 %
(1) CORN OIL	41.65%
(2) WHITE PETROLATUM	53.9 %
(3) NON-IONIC LANOLIN DERIVATIVES (e.g. AMERCHOL CAB)	1.96%
(4) CHLOROBUTANOL (ANHYDROUS)	0.49%
TOTAL	100.0 %

Equivalent compositions comprising 0.1, 0.5 and 1% cyclosporin (e.g. Ciclosporin) may be prepared by increasing each of the components (1) to (4) together by the required proportional amount.

The composition, which is in the form of an ointment, may be prepared by standard techniques, for example, by adding (1) to (2) and heating to about 35° to 60°C to form a clear liquid, then dissolving (3) and (4) with stirring in the clear liquid to form the vehicle for the ointment. The Ciclosporin is dissolved by stirring in the liquefied vehicle, after which the ointment is ready for final processing. Alternatively, the Ciclosporin can be dissolved in (1) or a portion of (1) and the obtained solution then added to the remaining ingredients before further processing. For production in large quantity the Ciclosporin is suitably dissolved in the mixture of (1) - (4) at elevated temperature using a high torque mixer. The obtained solution is then filtered asceptically and filled under sterile conditions into containers, e.g. ointment tubes, suitably containing up to ca. 5g, e.g. 3.5g ointment per container.

In production, compositions of the invention are preferably subjected to filtration, e.g. asceptic filtration, on completion of dissolution of the cyclosporin and before further processing.

For therapeutic use, compositions of the invention will preferably be filled into containers appropriate, e.g. adapted, devised or intended, for direct topical opththalmic application of the contents, for example ointment tubes as aforesaid having a closeable outlet of relatively small diameter and permitting ready application of the contents to or at the surface of the eye, e.g. in an amount of from about 0.05 to about 0.2 ml, e.g. of about 0.05 to about 0.1 ml.

Utility of the compositions of the invention may be demonstrated in animal test models, e.g. as hereinafter described, or in clinical trials.

TEST METHOD

The objective of the method is to determine the penetration into and reservoirs of radioactivity in various tissues of the rabbit eye, as well as systemic concentrations following a single topical application of compositions comprising tritiated Ciclosporin ("Ci-3H"), by investigation of distribution of Ci-3H in the eye tissues and obtained Ci-3H blood levels (systemic concentrations).

Ci-3H is prepared by introducing a tritium label at amino acid residue 1 (-MeBmt-) of Ciclosporin by standard techniques, for example, as described in Voges et al., "Synthesis and Applications of Isotopically Labeled Compounds", Ed. R.R. Muccino, Elsevier Press Amsterdam, 371-376 (1986), in the article entitled "Tritiated Compounds for In-Vivo Investigation". Purity and identity are established by NMR spectroscopy, TLC/radio-TLC, and reverse-phase HPLC. A 1:10 dilution of Ci-3H with unlabeled Ciclosporin is used for testing.

For testing, female New Zealand white rabbits (Lab Rab Co.) weighing 4 to 6 kilograms are used. The animals are housed in standard rabbit cages, fed a controlled diet (Purina Chow) and allowed water ad libitum. For approximately one hour following application of test composition, the rabbits are kept in a normal upright position in a restrainer. Test compositions are administered in 20 µl or 19.9 mg dosages using a calibrated pipette.

Pipettes are carefully filled so that there are no air bubbles, and test composition is carefully expelled into the cupped inferior cul-de-sac of both rabbit eyes. The lids are then held together gently for one second and released. The eyes are visually monitored for any signs of irritation, irritation induced tearing or opacity in accordance with the Calgon modification of the Draize test using a dissection lamp instead of a slit lamp (Draize, J.H., Appraisal for the Safety of Chemicals in Foods, Drugs and Cosmetics, association of Food and Drug Officials of the United States, Texas State Department of Health, Austin, Texas, 1959. Modified by Calgon Consumer Products

Research Labs, Toxicology, 1973.).

After dosing, groups of 3 rabbits are sacrificed at 0.3, 1, 2, 4, 6, 12, 24, 48 and 96 hours. Just prior to sacrifice, blood samples are obtained from the marginal ear vein. The animals are then sacrificed by injection of T-61 Euthanasia Solution (Hoechst) into the marginal ear vein. Both eyes are rinsed with normal saline (0.9%NaCl) and enucleated without rupturing surrounding blood vessels. The ocular surface is carefully rinsed and dried with filter paper to remove any drug remaining in the tear fluid. The aqueous humor is removed by means of a 26 gauge 3/8 inch needle attached to a 0.2 milliliter (ml) pipette inserted at the corneal limbus. The cornea is excised at the limbus, folloving which the iris and ciliary body are dissected as a single sample. The lens is then removed, and an aliquot of the vitreous is collected. Excess vitreous is removed from the remaining tissues by blotting with filter paper. The choroid-retina is scraped from the sclera, and a sample of the sclera is taken from the section closest to the optic nerve. To avoid contamination, clean instruments are used for the dissection of individual tissues. Each sample is rinsed and blotted on filter paper before being weighed into combustion cones. Blood samples (~200 µl) are also weighed into combustion cones. The tissue and blood samples are air-dried prior to combustion in a Packard Tri-Carb® Sample Oxidizer, Model 306 using Monophase®-40 (Packard Instrument Co.). Following combustion, the radioactivity of the samples is determined by scintillation counting in a Packard Tri-Carb® Liquid Scintillation Spectrometer, Model 460.

To determine specific activity, a 2.0 µl aliquot of test composition is dissolved in 100 ml of t.-butyl methyl ether, and 0.1 ml of the ether solution is assayed by the combustion method. Using the specific activity, the disintegrations per minute per gram (dpm/g) concentration of radioactivity in the tissues is converted to nanogram equivalents of Ciclosporin/gram of tissue or blood.

Radioactivity of all samples is determined within a statistical error of 7% at a confidence level of 95%. This implies that any net counts

per minute (cpm) value less than 3 would not be significantly different from zero and corresponds to a detection limit of 34 picograms per gram (pg/g).

In one series of trials employing the above test methodology, the following compositions are compared:

TEST COMPOSITION A: Composition of Example 1 in accordance with the present invention.

TEST COMPOSITION B: Comparative composition, comprising Ciclosporin and components (2) to (4) in the same amounts as in Example 1 and 41.65% mineral oil in place of corn oil as component (1).

TEST COMPOSITION C: Comparative composition comprising 2% Ciclosporin and 98% castor oil.

(For the purposes of filling COMPOSITION B into pipettes, the composition is first warmed to 30°C to facilitate filling and then allowed to cool to room temperature before application.)

RESULTS

Figures 1 to 7 attached provide graphical representations for variation in concentration of radioactivity in each of the assayed eye tissues with time. In each graph, time is plotted along the abscissa (horizontally) in hours up to 96 hours: concentraion is plotted along the ordinate (vertically) in mg Eq of Ciclosporin/g of tissue, all values being normalised to a dose of 0.335 mg Ciclosporin/eye.

Results for composition A are represented by plots with solid circles. Results for composition B are represented by plots with solid squares. Results for composition C are represented by plots with open inverted triangles.

Fig. 1 provides results for the aqueous humor.
Fig. 2 provides results for the cornea.
Fig. 3 provides results for the iris/ciliary.
Fig. 4 provides results for the lens.
Fig. 5 provides results for the vitreous.
Fig. 6 provides results for the choroid/retina.
Fig. 7 provides results for the sclera.

Figs. 1 to 7 indicate a fairly rapid initial absorprion of Ciclosporin with all three formulations into the anterior and posterior tissues of the eye. However, peak concentrations in the cornea (Fig. 2), which appears to serve as a reservoir for other intraocular tissues, was achieved ca. 3x as rapidly with composition A (ca. 2 hrs.) as compared with composition B (ca. 6 hrs.). Moreover, concentrations achieved in the cornea with composition A are markedly higher than with composition B. Composition C requires ca. 12 hours to achieve maximum concentration in the cornea.

The resultant and surprising increase in delivery to the deeper tissues of the eye is confirmed by results for the aqueous humor (Fig. 1) where the achieved AUC (area under curve) for composition A for the 96 hour period is ca. 2x that achieved with composition B and >3x that achieved with composition C. [Actual AUC (96hr.) values (mg Eq/g normalised to 0.335 mg/eye = composition A - 636: composition B - 334: composition C - 188.] The same pattern of advantage for composition A is maintained with respect to the iris/ciliary (Fig. 3) and the lens (Fig. 4).

Composition A is thus seen to be markedly and surprisingly superior to both compositons B and C with respect to delivery to anterior regions of the eye, in particular the cornea and to the aqueous/iris/ciliary. Compositions of the invention are thus of particular advantage in the treatment of diseases or conditions of the eye affecting or as they affect these regions, for example, for use in relation to corneal transplant, to the treatment of uveitis and of kerotoconjunctivitis sicca.

As regards the posterior segment of the eye, while superiority of composition A is less marked with respect to the vitreous and sclera (Figs. 5 and 7), it is notably superior in relation to the choroid/retina (Fig. 7), regions of the eye more typically involved in autoimmune diseases affecting or as they affect the posterior segment. Thus composition A provides markedly superior peak delivery as well as superior and better sustained total delivery to the choroid/retina. Thus a recorded AUC value (96hr) in the choroid/retina (mg Eq/g normalised to 0.335 mg/eye) for composition A is 527 as compared with values of only 296 and 184 for compositions B and C respectively.

Composition A is thus further markedly and surprisingly superior to both compositions B and C with respect to delivery to the posterior segment of the eye, including the choroid/retina and is thus of particular advantage in the treatment of diseases and conditions of the eye affecting or as they affect these regions, for example for use in the treatment of posterior uveitis as well as other immune mediated or inflammatory retinopathies.

As will be noted from Figs. 1 to 7, comparative composition C is in all respects markedly inferior to both compositions A and B.

The following table provides determined data for Ciclosporin blood level (systemic) concentrations. (ng Eq/g normalised to 0.335 mg/eye).

TIME (hrs)	COMPOSITION A	COMPOSITION B	COMPOSITION C
0.5	0.05 ± 0.04	0	0.12 ± 0.12
1	0.97 ± 1.09	1.36 ± 0.56	0.04 ± 0.04
2	1.56 ± 0.71	0.28 ± 0.61	0.44 ± 0.17
4	1.25 ± 0.88	0.87 ± 1.68	0.71 ± 0.11
6	0.27 ± 0.23	0.07 ± 0.19	0.84 ± 0.48
12	0	1.30 ± 3.52	0.46 ± 0.27
24	0	0.57 ± 1.55	0.63 ± 0.50
48	0	0.12 ± 0.34	0.81 ± 0.84
96	0	0	0.18 ± 0.05
AUC (0-96h)	5.96	30.68	54.49

As will be seen, systemic levels measured are relatively low for all three test compositions, but surpringly so for composition A in comparison with both B and C. Composition A thus appear as markedly superior both in terms of delivery to the eye and its tissues as well as in avoidance of systemic involvement.

Visual observation of the eye treated with composition A in the modified Draize test showed no composition related irritation.

The advantageous therapeutic properties of the compositions of the invention may also be demonstrated in clinical trials, for example on administration to subjects exhibiting disease or conditions of the eye as hereinabove set forth.

For the purpose of such trials, or for practical therapeutic use, e.g. in the treatment of uveitis (anterior or posterior), vernal conjunctivitis, vernal keratoconjunctivitis or keratoconjunctivitis sicca, composition of the invention, e.g. the composition of example 1, are suitably administered at or to the surface of the eye in individual amounts e.g. of from ca. 0.1 to 0.2 ml from 1 to 4x daily, e.g. depending on the particular disease or condition to be treated, its clinical status and the effect desired. Marked improvement in

condition as compared with e.g. untreated controls are observable with continuance of treatment, e.g. over a period of 1 to 2 weeks and upwards. The compositions of the invention are found to be well tolerated by subjects undergoing therapy, with no significant or untoward irritation.

In accordance with the foregoing and in a further series of embodiments the present invention also provides:

B) An ophthalmic composition as defined under (A) above in a container appropriate for ophthalmic application of said composition, e.g. as hereinbefore described, for example appropriate for application of said composition to or at the surface of the eye, e.g. to the cornea or corneal epithelium;

C) A process for the production of an ophthalmic composition as defined under (A) above, which process comprises bringing a cyclosporin into intimate admixture, appropriately with the application of warming, e.g. to a temperature of from about 30° to about 60°C, with component (1) and component (2) and, optionally, a component (3) and a component (4) as hereinbefore defined, and optionally thereafter filling the obtained composition into an appropriate container, e.g. as defined for (B) above;

D) A method of treating a disease or condition of the eye or of the surrounding or associated organs or tissues in a subject in need thereof, in particular of treating immune mediated or inflammatory diseases or conditions of the eye or of the surrounding or associated organs or tissues, which method comprises administering a composition as defined under (A) above topically to the eye, e.g. to or at the surface of the eye, e.g. to the cornea or corneal epithelium; as well as

E) A composition as defined under (A) above for use in a method as defined under (D) above, or a cyclosporin for use in the preparation of a composition as defined under (A) above, said

composition being for use in a method as defined under (D) above.

Particular sections, segments or tissues of the eye to which the method (D) is applicable are as hereinbefore described. Particular diseases or conditions of the eye to which the method (D) is applicable are similarly as hereinbefore described.

CLAIMS

1. An ophthalmic composition comprising a cyclosporin as active ingredient and comprising (1) an ophthalmically acceptable vegetable oil and (2) an ophthalmically acceptable petroleum jelly as carrier medium.

2. A composition according to claim 1 wherein the cyclosporin is Ciclosporin.

3. A composition according to claim 1 wherein the cyclosporin is [Nva]^2-Ciclosporin.

4. A composition according to any one of claims 1 to 3 wherein the cyclosporin is present in an amount of from about 0.01 to about 10%.

5. A composition according to claim 4 wherein the cyclosporin is present in an amount of from about 0.05 to about 5%.

6. A composition according to claim 5 wherein the cyclosporin is present in an amount of from about 0.1 to about 2.5%.

7. A composition according to claim 6 wherein the cyclosporin is present in an amount of about 0.1, 0.5, 1.0 or 2.0%.

8. A composition according to any one of claims 1 to 7 wherein component (1) is present in an amount of at least 25%.

9. A composition according to claim 8 wherein component (1) is present in an amount of from about 25 to about 65%.

10. A composition according to claim 9 wherein component (1) is present in an amount of from about 25 to about 45%.

11. A composition according to claim 10 wherein component (1) is present in an amount of from about 35 to about 45%.

12. A composition according to claim 11 wherein component (1) is present in an amount of from about 40 to about 45%.

13. A composition according to any one of claims 1 to 12 wherein component (2) is present in an amount of at least 25%.

14. A composition according to claim 13 wherein component (2) is present in an amount of at least 50%.

15. A composition according to claim 13 or 14 wherein component (2) is present in an amount of up to about 65%.

16. A composition according to claim 15 wherein component (2) is present in an amount of from about 50 to about 60%.

17. A composition according to claim 16 wherein component (2) is present in an amount of from about 50 to about 55%.

18. A composition according to any one of claims 1 to 17 wherein components (1) and (2) are present in a ratio of from about 1:2 to 2:1 p.p.w.

19. A composition according to any one of claims 1 to 18 wherein component (1) comprises olive, arachis, corn, castor or sesame oil.

20. A composition according to claim 19 wherein component (1) comprises corn oil.

21. A composition according to any one of claims 1 to 20 wherein component (2) comprises a white petrolatum.

22. A composition according to any one of claims 1 to 21 additionally comprising (3) an ophthalmically acceptable emulsifier.

23. A composition according to claim 22 wherein component (3) comprises a non-ionic lanolin derivative or extract.

24. A composition according to claim 23 wherein component (3) comprises a lanolin alcohol.

25. A composition according to claim 22 wherein component (3) comprises a sterol-based emulsifier.

26. A composition according to any one of claims 22 to 25 wherein component (3) is present in an amount of from about 0.5 to about 10%.

27. A composition according to claim 26 wherein component (3) is present in an amount of from about 0.5 to about 5%.

28. A composition according to claim 27 wherein component (3) is present in an amount of from about 1.0 to about 2.5%.

29. A composition according to any one of claims 1 to 28 additionally comprising (4) a preserving agent.

30. A composition according to claim 29 wherein component (4) comprises chlorobutanol.

31. A composition according to claim 29 or 30 wherein component (4) is present in an amount of up to about 5.0%.

32. A composition according to claim 31 wherein component (4) is present in an amount of up to about 2.0%.

33. A composition according to claim 31 or 32 wherein component (4) is present in an amount of from about 0.01%

34. A composition according to claim 33 wherein component (4) is present in an amount of from about 0.1 to about 1.0%.

35. A composition according to any one of claims 1 to 34 in a container appropriate for topical ophthalmic application of said composition.

36. A method of treating a diesease or condition of the eye or of the surrounding or associated organs or tissues in a subject in need thereof, which method comprises administering a composition according to anyone of claims 1 to 35 topically to the eye.

37. A method according to claim 36 for the treatment of a disease or condition affecting the anterior or posterior segment of the eye.

38. A method according to claim 36 for the treatment of a disease or condition of the eye affecting the cornea, the aqueous, the lens, the iris, the ciliary, the choroid or the retina.

39. A method according to any one of claims 36 to 38 for the treatment of an autoimmune or inflammatory disease or condition of the eye or disease or condition of the eye comprising undesirably elevated immuno-response or inflammatory reaction or event as part of its etiology.

40. A method according to any one of claims 36 to 38 for the treatment of anterior or posterior uveitis, chronic keratitis, keratoconjunctivitis sicca, vernal keratoconjunctivitis, conjunctivitis, including vernal conjunctivitis, or in keratoplasty.

41. A composition as claimed in any one of claims 1 to 35 for use in a method as claimed in any one of claims 36 to 40.

42. A cyclosporin for use in the preparation of a composition as claimed in claim 41.

43. A composition, method or cyclosporin according to any one of claims 1 to 42 substantially as hereinbefore described in particular with reference to the accompanying examples.

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